The Systematic Screening and Management of Hypothyroidism and Hyperthyroidism During Pregnancy

Daniel Glinoer

Altogether, thyroid function abnormalities during pregnancy can affect up to 10% of all women. The high prevalence of both hypo- and hyperthyroidism, the obstetrical repercussions associated with thyroid dysfunction in the mothers, as well as the potential role of maternal thyroid dysfunction as an influence on fetal development constitute solid arguments for a further increase of our knowledge of the pathophysiological processes underlying the alterations of thyroid function related to the pregnant state. In this review, the focus will be on the most clinically relevant aspects associated with hypothyroidism [autoimmune thyroid disorders (AITDs), subfertility, risk of miscarriage, risk of hypothyroidism in women with AITD and treatment of hypothyroid women] and with hyperthyroidism (clinical presentations during pregnancy, Graves' disease and its management, fetal hyperthyroidism in women with antithyroid-stimulating hormone receptor antibodies and gestational transient thyrotoxicosis associated with human chorionic gonadotropin stimulation of the maternal thyroid gland). I also propose a global strategy for the systematic screening of hypo- and hyperthyroidism in the pregnant state.

• Hypothyroidism and Pregnancy

Hypothyroidism (HO) in the General Population

Twenty years ago, a representative sample of an entire adult community was surveyed for thyroid disease, and in particular for thyroid insufficiency, in the northeastern part of England (the Whickham study) (Tunbridge *et al.* 1977). Even today the Whickham study remains a unique example, and other surveys carried out with different methodological approaches and in different parts of the world have largely corroborated the main findings of the original survey (Wang and Crapo 1997). Globally, these studies have shown that the prevalence of HO is high in the population (1–10%), that it remains frequently undiagnosed (subclinical), and that it is mainly a female disorder. The main cause of HO is chronic autoimmune thyroid disease (AITD), and the prevalence of antithyroid antibodies is closely associated with aging in the female population (6% below 45 years of age; 10% between 45 and 75 years; >15% over 75 years); in parallel, the prevalence of HO increases with aging. Recently revisited in a follow-up study, the original Whickham survey has yielded another major finding, namely, that the incidence of overt HO is at least four cases per 1000 women per year, with a close association between the rise in thyroid-stimulating hormone (TSH) and positive antithyroid antibodies (Vanderpump *et al.* 1995). Hence, because of its high frequency in the young population and its female preponderance, it is logical to consider whether HO might both affect pregnancy and its course be affected by pregnancy.

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Fertility and Pregnancy Outcome in Hypothyroid Women

There is a known association between HO and decreased fecundity which, in most instances, is primarily associated with ovulatory disturbances and not with miscarriage: women who require treatment with thyroid hormone have a twofold greater risk of primary ovulatory infertility (Garber 1997).

When hypothyroid women do become pregnant, they have an increased risk of obstetrical complications (such as intrauterine fetal demise, gestational hypertension, placental abruption and poorer perinatal outcome). Several studies have indicated that adequate thyroid hormone administration greatly improves, although it does not entirely suppress, the frequency of these abnormalities (Montoro *et al.* 1981). In general, infants of hypothyroid mothers appear healthy, without evidence of thyroid dysfunction, provided that no iodine deficiency was present *in utero*. Some studies, although not confirmed by all, have indicated that infants born to hypothyroid mothers might have an increased risk of a higher perinatal mortality and congenital malformations, and of a lower birth weight. The causal relationship is, however, difficult to ascertain, as other medical problems might be associated with HO, such as anemia or nutritional inadequacy. Finally, severe HO during pregnancy raises evident concern about potential long-lasting, psychoneurological consequences for the progeny, related to insufficient transplacental transfer of maternal thyroid hormones to the developing fetus during the first half of gestation, before the fetal thyroid gland becomes functional (Porterfield and Hendrich 1993).

AITD and the Risk of Miscarriage

Since the early 1990s, several studies have shown an increased prevalence of spontaneous abortion in apparently euthyroid pregnant women who have antithyroid antibodies (Stagnaro-Green 1990) (Fig. 1). Altogether, these studies have indicated: (1) that the risk

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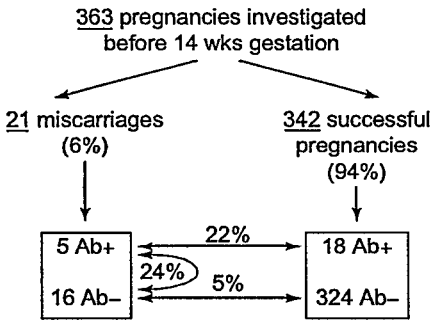

Figure 1. Between 1988 and 1990 in our institution, a large group of consecutive euthyroid pregnant women was investigated prospectively and systematically for the presence of antithyroid autoantibodies and the occurrence of spontaneous abortion before 14 weeks of gestation. While the overall rate of miscarriage was 6% in the cohort, the prevalence of autoimmune thyroid disorders (AITD) reached 24% among those women with a miscarriage. Furthermore, among women with AITD, the prevalence of a miscarriage reached 22%, which was significantly increased compared with the 5% prevalence of spontaneous abortion in the antithyroid antibody negative group (p <0.005) (adapted from Glinoer *et al.* 1991). Ab+, positive for antithyroperoxidase and/or antithyroglobulin autoantibodies; Ab–, negative for both autoantibodies.

occurs primarily in the first trimester of gestation; (2) that the miscarriage rate is increased two- to fourfold compared with women without detectable thyroid immunity; (3) that the risk of miscarriage is further amplified in women who have a history of consecutive abortions (three or more); and (d) that these women present no clear evidence of hypothyroidism, even though in some instances borderline high serum TSH levels have been demonstrated. The presence of thyroid immunity is an independent marker of an at-risk pregnancy, and is not linked directly to other autoimmune disturbances, such as positive anticardiolipin, antinuclear or antiphospholipid antibodies (Bakimer *et al.* 1994).

Can the association between thyroid immunity and an increased risk of fetal wastage owing to early miscarriage be explained? The easiest explanation is that the presence of thyroid antibodies reveals a more generalized underlying abnormal stimulation of the immune system (Geva *et al.* 1997). However, other explanations cannot at present be ruled out, and the question clearly requires further investigation. For example, it could be speculated that mild degrees of thyroid insufficiency (difficult or impossible to detect by serum hormone measurements) might play a role locally at the level of the female genital tract. In addition, it has been our experience that women with AITD are two to three years older on the average when becoming pregnant, compared with control subjects from the same cohort, and the age difference is statistically significant (Glinoer *et al.* 1991). Therefore, it is possible that thyroid immunity acts by hindering fecundity, hence delaying conception. This hypothesis, even though not proven to date, might have clinical relevance, as it has been established clearly that the risk of having a spontaneous miscarriage increases significantly with age (Knudsen *et al.* 1991).

AITD and the Risk of Hypothyroidism in the Pregnant State

Between June 1990 and December 1992, 1660 consecutive pregnancies, with no previous history of thyroid disorder, were investigated systematically for the presence of antithyroid antibodies, and for the occurrence of alterations in serum TSH and free T_4 concentrations (Fig. 2). The prevalence of AITD was 6.5%, which is the expected prevalence among female subjects of child-bearing age. Among these patients, 16 women were biochemically hypothyroid (serum TSH >4 mU l^{-1}) and four were hyperthyroidic (with both suppressed TSH and supranormal free T_4). These 20 cases will be discussed later. Eighty-seven women (5.2%) showed the presence of antithyroid antibodies at the time of the initial visit, but free T_4 and TSH concentrations were in the normal range. Thyroid function was monitored sequentially during gestation. Despite the expected decrease in the titers of antithyroid antibodies during gestation, the parameters of thyroid function showed a gradual deterioration towards HO in a significant fraction of women. Already during the first trimester, the distribution curve of serum TSH was shifted significantly towards higher (albeit still normal) values when compared with normal pregnant controls from the same cohort. At the time of delivery, 40% of women with AITD had a serum TSH >3 mU l^{-1}, with almost half of them >4 mU l^{-1}. Hence, in the early stages of pregnancy, women with AITD were able to maintain normal thyroid function owing to the sustained thyrotropic stimulation. Three days after delivery, however, their serum-free T_4 concentrations were markedly lower than those of controls: on average, there was a 30% reduction in serum-free T_4, with almost a half of AITD women in the HO range, confirming that these women have a reduced functional thyroid reserve. An important observation was that it was possible, at the individual level, to predict progression to HO on the basis of serum TSH levels and thyroid antibody titers in the first trimester (Glinoer *et al.* 1994).

Subclinical and Overt Hypothyroidism During Pregnancy

When HO does not result from the previous treatment of hyperthyroidism with radioiodine or surgery, the most common cause of primary HO in women of child-bearing age is chronic autoimmune thyroiditis, which occurs in both goitrous and atrophic forms. Population-based studies have indicated that as many as 2.5% of all pregnancies might have undiagnosed subclinical HO (Klein *et al.* 1991). In our studies, a similar prevalence of 2.2% undiagnosed HO was found, with serum TSH ranging between 4 and 20 mU l^{-1}; in addition, free T_4 concentrations, even though not systematically subnormal, tended to cluster near the lower limits of normal. These women, diagnosed in the early stages of gestation by systematic screening, were treated with T_4 (50–125 μg day^{-1}) throughout gestation, resulting in a normalization of thyroid function. In 16 of the 41 women diagnosed with subclinical HO, the etiology was clearly related to AITD, with antithyroperoxidase antibody (TPO-Ab) titers between 400 and 5000 U ml^{-1}. In the remaining cases, the etiology could not

be attributed to AITD, in the absence of detectable antithyroid antibodies or a family history of goiter or HO (Glinoer 1997).

In relation to thyroid hormone replacement during pregnancy for women with a previously established diagnosis of primary HO, several studies carried out during the past ten years have indicated the need for a systematic adjustment of the T_4 replacement dose. The most comprehensive study was reported by Kaplan (1992). In a retrospective analysis of thyroid hormone requirements in a group of 65 women who were hypothyroid because of Hashimoto's thyroiditis or previous thyroid ablation for hyperthyroidism, the author showed that serum TSH rose markedly when thyroxine replacement doses were maintained at prepregnancy levels. Moreover, free T_4 concentrations decreased (on the average by 40%) and became subnormal in 13% of the women. In contrast, raising the daily thyroxine dosage by 40–100 μg day^{-1} resulted in a normalization of serum TSH. After parturition, the T_4 requirements returned approximately to the prepregnancy dosage. The study also showed that the increment in T_4 dosage required to maintain euthyroidism during pregnancy depended upon the etiology of HO: women with AITD had a residual thyroid secretory capacity allowing them to adapt (although insufficiently) to the changes in hormone requirements associated with pregnancy, while women with a previous thyroid ablation were incapable of adaptation to those changes, hence requiring a greater increment in the thyroxine dosage to remain euthyroid.

The following consensus guidelines have been proposed for the care and management of hypothyroid women during pregnancy (Glinoer 1997). First, the daily dose of T_4 should be increased in at least 80% of hypothyroid women. Pregnant women who do not require such an increase in dosage were probably overtreated before becoming pregnant. Second, the increased need for T_4 is already apparent in the first trimester of gestation,

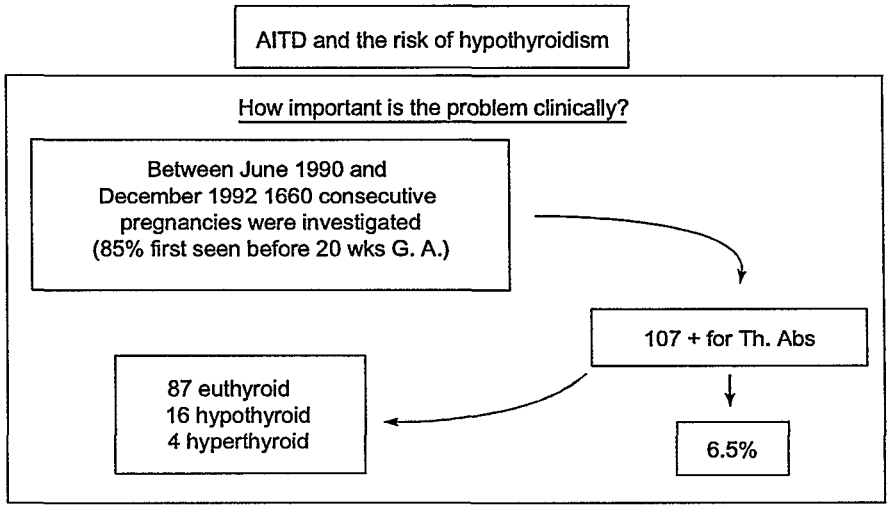

Figure 2. Prospective assessment of the prevalence of thyroid dysfunction and autoimmune thyroid disorders (AITD) in a population of consecutive healthy pregnant women (with no previous history of thyroid disease or treatment), based on the determination of thyroid function parameters and antibody detection at the time of the initial visit. Antithyroid antibodies were found in 6.5% of the cohort, with 5.2% being clinically and biochemically euthyroid, and 1.3% presenting thyroid dysfunction, associated with thyroid immunity, in the early stages of gestation.

concomitant with major changes in thyroidal economy associated with pregnancy. Hence, the adjustment of T_4 dosage should be accomplished without delay, in the early stages of gestation. Third, the required hormone increments vary widely (between 10% and 150%), with a median dosage increment of 40–50% over the pregestational replacement T_4 dosage. Therefore, each case needs to be assessed individually. Fourth, a regular clinical and laboratory follow-up is essential, with periodic determinations of TSH and free T_4 concentrations, indicating the mandatory need for a close collaboration between the endocrinologist and the obstetrician.

Systematic Screening for AITD and Hypothyroidism During Pregnancy

It is justifiable to propose a systematic screening for HO during pregnancy for the following reasons: (1) both AITD and hypothyroidism are common in young female subjects, (2) subclinical HO often remains undiagnosed, and (3) potentially specific obstetrical risks are associated with HO. In addition, there is a rationale for proposing the systematic detection of AITD during pregnancy, based on the following arguments: (1) the increased risk of spontaneous abortion in women with AITD; (2) the risk of progressive HO in euthyroidic women with antithyroid antibodies; (3) the risk of postpartum thyroiditis in the year following pregnancy (50% of AITD women display biochemical evidence of thyroid dysfunction); and (4) the well-known, long-term risk of developing definitive HO later on in life in women with chronic autoimmune thyroiditis.

The following scheme could be proposed (Fig. 3). As a first step, serum TSH and thyroid antibodies are measured as early as possible, preferably between 12 and 20 weeks of gestation. Ideally, both antithyroglobulin antibody (TG-Ab) and TPO-Ab titers should be measured. However, if for economical reasons only one thyroid antibody can be assessed, screening with TPO-Ab is to be preferred, because it yields the best diagnostic score, TPO-Ab being positive in 75–80% of women with AITD. If serum TSH is below 2 mU l^{-1} and thyroid antibodies are negative, nothing more needs to be done. If serum TSH concentrations are above 4 mU l^{-1}, irrespective of the positivity or negativity of antithyroid antibodies, the subject

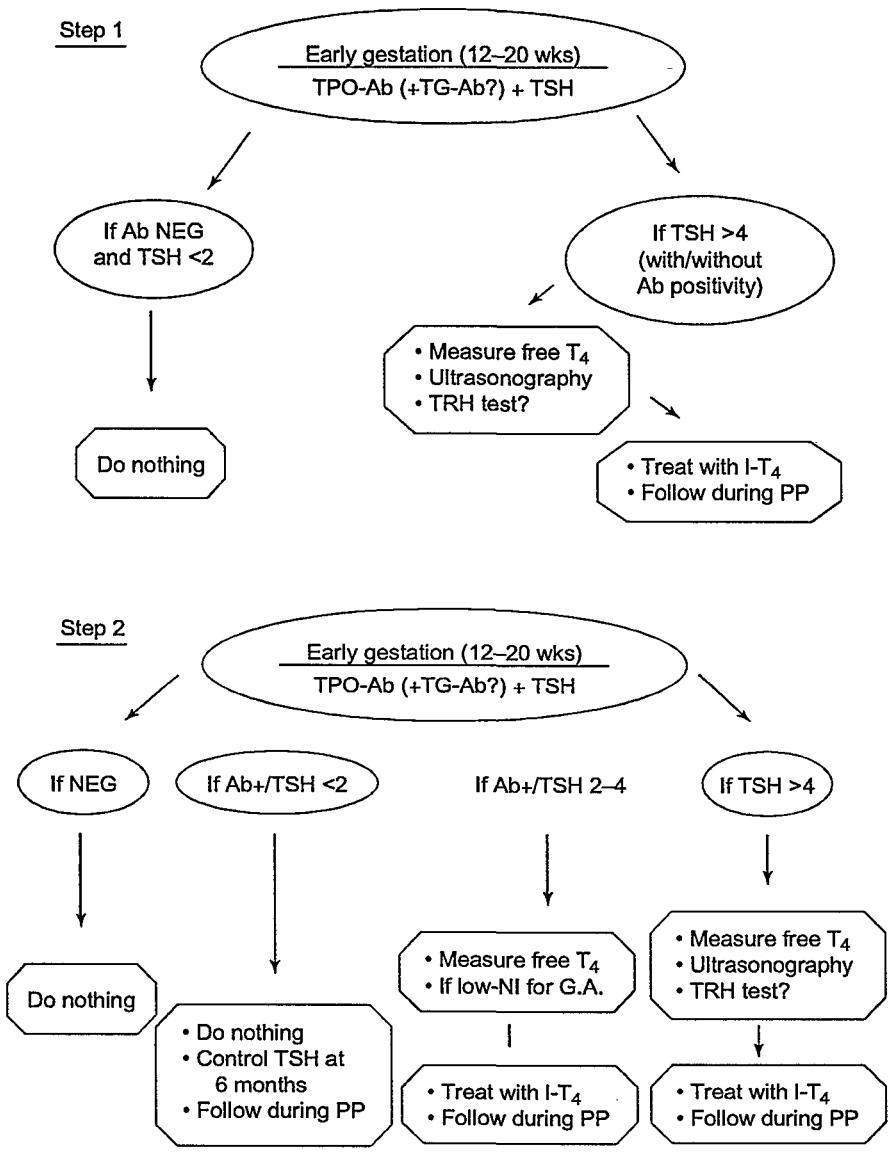

Figure 3. A proposed two-step algorithm for the systematic screening of autoimmune thyroid disorders (AITD) and hypothyroidism during pregnancy, based on the determination of antithyroperoxidase antibodies (TPO-Ab), antithyroglobulin antibodies (TG-Ab), and serum thyroid-stimulating hormone (TSH) concentrations in the first half of gestation.

should be considered hypothyroid. We propose determination of free T_4 concentrations, ultrasonography of the thyroid gland (in search of glandular hypotrophy) and, possibly, in specific cases, a thyrotropin-releasing hormone (TRH) test. Based on these results, women should be treated with T_4 throughout pregnancy and thyroid function parameters should be monitored every two to three months. Obviously, such women should also be followed during the postpartum period.

The second step in the algorithm concerns the women with positive antithyroid antibodies. In this setting, we propose that treatment should be based on serum TSH levels during early gestation. When serum TSH is below 2 mU l^{-1} (most often associated with low titers of antithyroid antibodies), systematic treatment with T_4 is not warranted. We propose that serum TSH should be monitored at six months gestation, and that women should be followed during the postpartum period. In contrast, for women with thyroid immunity and serum TSH concentrations within the normal range, but already between 2–4 mU l^{-1} during early gestation (most often associated with higher thyroid antibody titers), we propose the measurement of free T_4 concentrations and, if they are low or low–normal for the gestational age, treatment with T_4 for the remainder of the pregnancy (usually, between 50 and 100 μg day^{-1}) will be sufficient to maintain normal thyroid function. Obviously, such women should also be followed during the postpartum period.

Future prospective studies are necessary to demonstrate the relevance of the proposed scheme, as there is not yet direct evidence of the advantages of treating subclinical hypothyroidism during pregnancy. However, indirect arguments suggest strongly that no harm can be done and treatment with thyroid hormone can only be beneficial.

- **Hyperthyroidism and Pregnancy**

Hyperthyroidism (HR) in the Community and in Pregnancy

The epidemiological characteristics of HR in the adult population present marked differences from those of HO. First, while HO is a relatively common disorder, HR occurs much less frequently, with an overall prevalence rate of 1–2% and estimated incidence rates of 0.1–0.8 per 1000 women per year (Wang and Crapo 1997). Second, while the risk of developing HO clearly increases with age, this is not the case for HR. The main age-related change for HR is the type of medical condition that causes the metabolic disorder: specifically, HR is most often of autoimmune origin in young patients, while it is more often related to toxic nodular disease in older patients. Third, as alluded to above, there is no clear association between aging, positive antithyroid antibodies and hyperthyroidism.

During pregnancy, HR is usually thought to occur in ~2 of every 1000

women (Becks and Burrow 1991). The causes of hyperthyroidism include the classic causes found in the general population, but also two others that are specific for the pregnant state (Table 1). Clinical entities such as toxic adenoma, multinodular toxic goiter, subacute or silent thyroiditis and thyrotoxicosis factitia are extremely uncommon. Molar disease should always be considered and can potentially lead to fulminant hyperthyroidism, particularly in women with a pre-existing autonomous nodular goiter. However, uncomplicated hydatidiform mole is now easily diagnosed in the early stages of gestation, and will therefore rarely lead to severe hyperthyroidism, because it lasts only for a few weeks or months and is cured rapidly by the removal of the pathological trophoblast (Hershman 1972). The major cause of hyperthyroidism in women of child-bearing age is Graves' disease (GD). In recent years, another cause has been characterized, resulting from the direct stimulation of the thyroid gland by human chorionic gonadotropin (hCG), which induces a transient – although also potentially severe – form of hyperthyroidism, and is observed in the first half of gestation. The syndrome, referred to as 'gestational transient thyrotoxicosis', has to be differentiated from GD, as the course of both conditions, the fetal risks associated with them, and the management and follow-up of both entities are different (Glinoer *et al.* 1993, Yoshimura and Hershman 1995).

Table 1. Hyperthyroidism in pregnancy

Numbers	*Prevalence*	*Author (year)*
Prevalence		
75 cases per 38 381 subjects	0.2%	Niswander *et al.* (1972)
35 cases per 9453 subjects	0.4%	Kamijo *et al.* (1990)
227 cases per 241 036 births	0.1%	Wing *et al.* (1994)
4 cases per 1660 subjects	0.2%	Glinoer (1995)
Causes		
Graves' disease	The three main etiologies of hyperthyroidism	
Molar pregnancy		
Gestational transient thyrotoxicosis		
Subacute thyroiditis	Rare causes of hyperthyroidism	
Toxic adenoma		
Multinodular toxic goiter		
Iodine-induced thyrotoxicosis		
Thyrotoxicosis factitia		

Hyperthyroidism complicating pregnancy is a rare, but potentially severe, condition occurring in ~1 per 2000 pregnancies.

GD in Pregnancy

The clinical diagnosis of GD is usually not difficult and can be confirmed readily by laboratory tests. Three clinical situations are important to consider: women with active GD diagnosed before pregnancy who are under antithyroid drug (ATD) treatment; women who are in remission or considered to be cured after previous ATD treatment, surgery, or radioiodine; and women in whom the diagnosis of GD was not established before pregnancy (presumably because they had never been ill), but who carry TSH-receptor antibodies (TSHR-Ab).

An important concept is that maternal and fetal outcome is related directly to the control of hyperthyroidism (Mestman 1997). For patients in whom the diagnosis is made correctly, early on in pregnancy, and treatment is started promptly, the prognosis for both the mother and the offspring is excellent; on the contrary, maternal and fetal complications are increased dramatically in patients who remain thyrotoxic during the second half of gestation (Drury 1986, Davis *et al.* 1989). Therefore, in mothers with GD, TSHR-Ab titers should be determined as early as possible in gestation (10–12 weeks), to evaluate the risk of fetal and neonatal hyperthyroidism (TSHR-Ab titers may remain elevated, even after thyroidectomy or thyroid ablation with radioiodine, or the apparent cure of GD with ATD several years before pregnancy). Raised TSHR-Ab titers stimulate both the maternal thyroid gland (provided that enough functional thyroid tissue remains), and, more importantly perhaps, the fetal thyroid gland, with fetal hyperthyroidism developing during the second half of gestation.

At a recent symposium held during the European Thyroid Association Meeting (Munich, September 1997), it was concluded that when TSHR-Ab titers are elevated in early gestation, they should be monitored, with a second determination being carried out at six months gestation. When antibody titers have not decreased substantially during the second trimester, the diagnosis of fetal hyperthyroidism should actively be sought. Fetal hyperthyroidism can be assessed from ultrasonographic data by the presence of a fetal goiter, tachycardia, growth retardation, increased fetal motility and accelerated bone maturation. In selected cases, fetal cord blood sampling might be required to determine fetal thyroid hormone concentrations and therapy with ATD initiated (Skuza *et al.* 1996, Polak *et al.* 1997).

Globally, in mothers with a good control of hyperthyroidism, the relative risk of fetal complications is only increased twofold, compared with a ninefold relative risk increase for untreated hyperthyroid mothers (Mestman 1997). A clear demonstration of the potential risk for the fetus was provided by Davis *et al.* (1989). Mothers treated for hyperthyroidism had an overall frequency of stillbirth, premature deliveries, malformations and thyroid crises amounting to 19%, which was not different from an unaffected

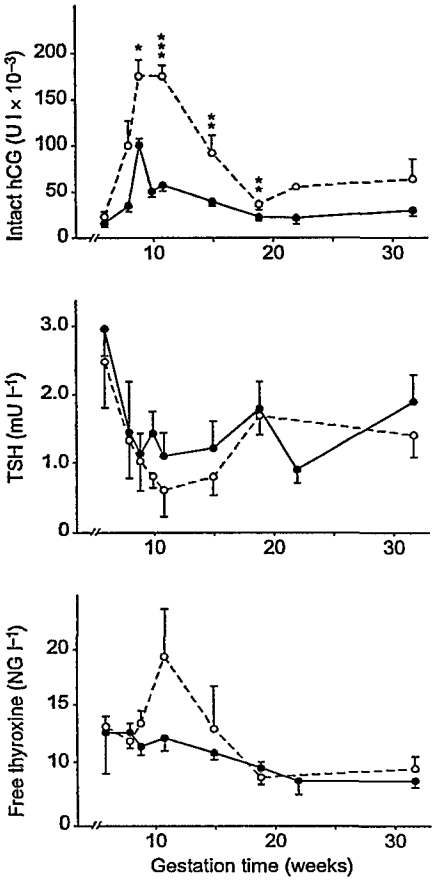

Figure 4. Profiles of changes in heterodimeric intact human chorionic gonadotropin (hCG) (upper graph), serum thyroid-stimulating hormone (TSH) (middle graph) and free T_4 (lower graph) levels as a function of gestational time in women with single (closed circle) (n = 17) and twin (open circle) (n = 13) pregnancies. Each point corresponds to the mean ± SD of individual serum samples obtained at each gestational age [modified with permission from Grün *et al.* (1997)].

population with a comparable socioeconomic status, while in untreated mothers, almost 100% of infants were affected by one of the above complications, prematurity alone representing 50% of them, as a result of the obstetrical repercussions of maternal hyperthyroidism (congestive heart failure, atrial fibrillation, pre-eclampsia, etc.).

In general, hyperthyroidism caused by GD tends to improve progressively during pregnancy, although exacerbations can be observed in early gestation. Three main reasons have been advocated to explain the 'spontaneous' improvement. Pregnancy is associated with partial immune suppression, thereby explaining a progressive decrease in antibody (and hence TSHR-Ab) titers (Geva *et al.* 1997). The rise in serum thyroxine-binding globulin (TBG) in the first trimester is associated with a significantly increased serum-binding capacity for thyroid hormones, which tends to decrease serum-free T_4 and T_3 concentrations. The obligatory iodine losses specific to the pregnant state tend to reduce iodine availability for the thyroid. Paradoxically, relative iodine deficiency might also be advantageous for pregnant patients with GD.

The classically favorable evolution of GD during pregnancy is, however, not an absolute feature: the decrease in TSHR-Ab titers is not always uniform, and exacerbations of hyperthyroidism also due to GD do occur in the first trimester, perhaps as the result of hCG-induced thyroidal stimulation (Amino *et al.* 1982, Tamaki *et al.* 1993).

The Management of GD in Pregnancy

As a summary of many studies dealing with GD in pregnancy, the following principles of 'good clinical practice' can be proposed for management (Hamburger 1992, Glinoer 1997, Mestman 1998).

When the diagnosis of GD has not been established before pregnancy, the disorder is not always readily suspected clinically, mainly because the symptoms and signs of mild to moderate hyperthyroidism may be mimicked by the hypermetabolic state of normal pregnancy. Attention should be given to a history of autoimmune thyroid disease in close family relatives, the presence of a goiter and/or suggestive eye signs, and a variety of clinical manifestations such as heat intolerance, warm and moist skin, tachycardia, wide pulse pressure, weight loss and excessive vomiting in the early stages of pregnancy. Thyroid function should also be assessed in all patients with hyperemesis gravidarum. Concerning the management of patients with GD diagnosed during pregnancy, the general rules of treatment are well defined. Patients should be treated exclusively with ATD, unless the severity of the condition (or side effects of medical treatment) justifies a more radical approach by surgery (preferably carried out in the second trimester). The optimal dosage of ATD should be maintained at a minimum, and the drugs discontinued whenever possible, which is often the case after four to six months gestation. One should not rely on T_4 administration to the mother to maintain euthyroidism in the fetus, as the transplacental passage of ATD is high, while it is negligible for thyroid hormones. Propylthiouracil, methimazole or carbimazole can be used, as long as the minimal dose rule is implemented. Maternal free hormone concentrations should be maintained in the upper third of the normal range, as such maternal levels are associated with fetal free hormone concentrations remaining in the midrange of normal values. Finally, women who require ATD treatment after parturition should be allowed to continue taking ATD, even during breastfeeding, as long as the daily dosage required remains relatively small (up to 30 mg methimazole or 150 mg propylthiouracil).

Gestational Transient Thyrotoxicosis (GTT)

Gestational hyperthyroidism of non-autoimmune origin occurring in women with a normal pregnancy has been clarified by recent reviews (Glinoer 1997, Mestman 1998). GTT differs from GD in that it occurs in women without a past history of GD and in the absence of detectable TSHR-Ab. GTT is not always clinically apparent because it is most often transient. Its etiology is related directly to the thyrotropic stimulation of the thyroid gland associated with hCG (Glinoer *et al.* 1993, Kimura *et al.* 1993, Tsuruta *et al.* 1995). Recent studies indicate that the prevalence of GTT might be as high as 2–3% of all pregnancies (ten times more frequent than hyperthyroidism caused by GD), if one considers the concept that, owing to its transient nature, the clinical manifestations of the disorder will not always be apparent or detected routinely.

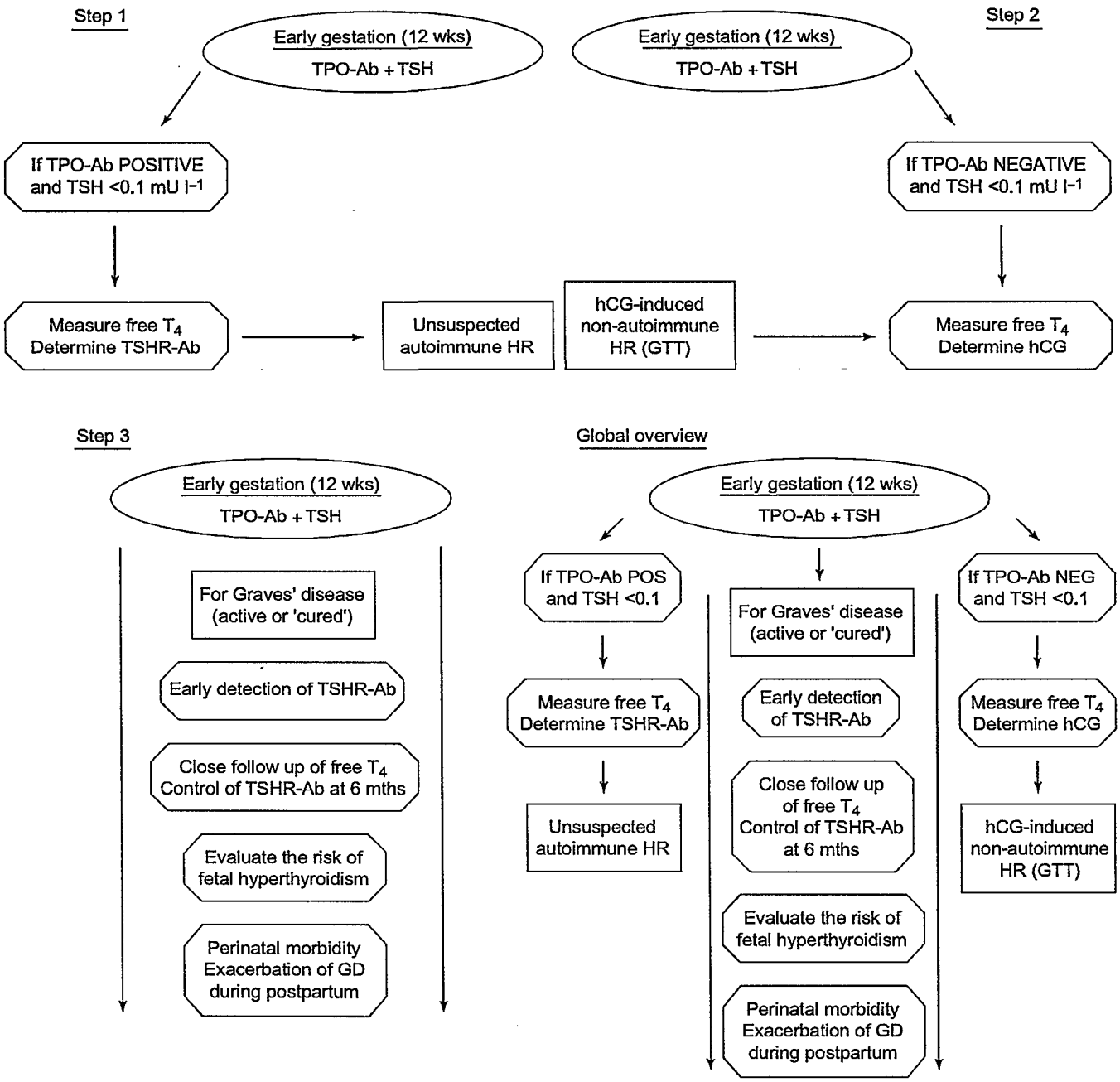

Figure 5. A proposed three-step algorithm for the systematic screening of thyroid hyperfunction during pregnancy, based on the data available from the screening for thyroid hypofunction (Fig. 3). The first step allows for the diagnosis of unsuspected hyperthyroidism of autoimmune origin; the second step for the diagnosis of gestational transient thyrotoxicosis (GTT); the third step concerns the patients with Graves' disease (active or considered cured). Adapted in part (with modifications) from Glinoer (1998).

Clinically, signs and symptoms compatible with hyperthyroidism, namely weight loss or the absence of weight increase, tachycardia and unexplained fatigue, are found in half of the women with GTT. Hyperemesis is frequently associated with the most severely thyrotoxic cases, and in some women the symptoms are sufficiently alarming to require hospitalization. Most women with GTT require no specific treatment, and the symptoms can be relieved by the administration of β-adrenergic blocking agents for a short period. In rare cases, the severity of the clinical presentation may lead to treatment with propylthiouracil (usually for only a few weeks). In all the

cases that we have seen, GTT was transient and the normalization of free T_4 concentrations paralleled the decrease in hCG concentrations. Also, GTT was not associated with a less favorable outcome of pregnancy.

Recently, we reported a study that reinforces the concept that normal women can develop transient hyperthyroidism associated with abnormally elevated hCG levels, particularly when the hCG rise is maintained for a prolonged period (Grün *et al.* 1997). Twin pregnancy is a clinical condition 'naturally' associated with abnormally high and sustained hCG concentrations. A group of women with twin pregnancies was investigated prospectively in the early stages of gestation for the occurrence of GTT. In this group, the gestational age was precisely known because conception had been obtained by *in vitro* fertilization techniques. This group was compared with a control group of single pregnancies obtained with the use of similar techniques (Fig. 4). The results indicated that peak hCG values were significantly higher in twin pregnancies (in fact, almost double), and of much longer duration. On average, hCG values >75 000 U l^{-1} lasted for less than a week in single pregnancy, while hCG levels >100 000 U l^{-1} (often reaching or exceeding 200 000 U l^{-1}) lasted for up to six weeks in the twin pregnancies. Thyroidal repercussions were in accordance with our hypothesis: twin pregnancy was associated with a more profound and frequent (threefold) blunting in serum TSH. Also, while free T_4 values remained unchanged in single pregnancy, they often rose transiently above normality in twin pregnancy, expressing the full picture of GTT.

The precise mechanisms underlying GTT, usually associated with elevated and sustained hCG values, are still not understood fully. It remains possible that abnormal molecular variants of hCG are produced in these situations, with a prolonged half-life explaining the sustained high levels, or hCG variants with a more potent thyrotropic activity (Tsuruta *et al.* 1995). It has also been proposed that a dysregulation of hCG production might occur transiently in such women, particularly for β-hCG production (which is the rate-limiting step in the formation of intact heterodimeric hCG at this stage of pregnancy). Given the example of twin pregnancy, a quantitative direct effect of raised hCG levels might be sufficient to explain GTT, provided that hCG values remain >75 000–100 000 U l^{-1} for a sufficient period of time to stimulate the thyroid gland. In other words, we believe that GTT is related directly to both the amplitude and duration of peak hCG. Whatever the final explanation, the effects of hCG in stimulating the thyroid gland can best be explained by the marked homology between both the hCG and TSH molecules, as well as between the luteinizing hormone (LH)/CG and TSH receptors (Vassart and Dumont 1992). In this view, GTT can be seen as an example of endocrine 'spill-over' syndromes, a novel concept based on molecular mimicry between hormone ligands and their receptors (Yoshimura and Hershman 1995).

Finally, GTT is often associated with nausea (morning sickness), increased vomiting and hyperemesis gravidarum, a severe condition requiring hospitalization and drastic treatment (Goodwin *et al.* 1992). Several studies have now established a correlation between the intensity of emesis and frequent abnormalities of thyroid function. Because there is no indication of increased vomiting among pregnant women with GD, hyperemesis in pregnancy appears to be associated with hCG-induced thyrotoxicosis, although evidently not all cases of vomiting during early pregnancy are related to disturbances of thyroid function.

Systematic Screening for Hyperthyroidism During Pregnancy

Based on the information reviewed above, hyperthyroidism is probably more frequent than is usually believed during pregnancy, when one takes into consideration the cumulative prevalences of hyperthyroidism related to both GD and GTT, which together may affect 3–4% of all pregnancies. We have recently proposed that there is at least a conceptual justification to organize the systematic screening for hyperthyroidism during pregnancy (Glinoer 1998). Because, as discussed earlier, AITD and hypothyroidism justify systematic screening, one could propose that a screening strategy for hyperthyroidism could be derived from the information gained by the screening for hypothyroidism in the pregnant state.

The general outline of such a scheme is shown in Fig. 5. The overall strategy is based on the availability of serum TSH values and TPO-Ab titers in early gestation, at around 10–12 weeks.

First, if TSH is suppressed (or blunted) and TPO-Ab positive, serum-free T_4 and TSHR-Ab should be determined. This branch of the algorithm allows for the diagnosis of cases with unsuspected underlying hyperthyroidism of autoimmune origin, broadly corresponding to three to five cases per year, given a hospital setting delivering 1000–1500 babies per year.

Second, if TSH is suppressed (or blunted) and TPO-Ab undetectable, free T_4 and hCG concentrations should be determined. This branch of the algorithm allows for the diagnosis of non-autoimmune, hCG-induced hyperthyroidism, corresponding to ~30 cases per year, given a similar hospital setting.

Third, concerning all women with a history of GD (present or past, active or considered cured), TSHR-Ab titers should be determined in a second step, and obviously also free T_4 concentrations when women have active (ATD-treated) GD before conception. In women with active disease, or 'metabolically' cured disease but in whom high titers of Graves' IgG are maintained, TSHR-Ab titers should be monitored at a later stage during gestation, preferably at the end of the second trimester. This strategy allows for the diagnosis of maternal autoimmunity related to GD, and also for the suspicion of fetal hyperthyroidism allowing, in turn, for the organization of the careful monitoring of fetal development.

Finally, all cases with autoimmune hyperthyroidism, suspected or diagnosed during pregnancy, require a

close monitoring of antithyroid antibody titers (both TPO-Ab and TSHR-Ab) and thyroid function during the first year postpartum, because of the significant risks of developing postpartum thyroiditis or a postpartum exacerbation of thyrotoxicosis.

- **Conclusions**

Despite considerable knowledge gained recently from several studies investigating the physiological adaptation of thyroid function during pregnancy, and a better characterization of the pathological alterations associated with the pregnant state, hypo- and hyperthyroidism in pregnancy continue to pose difficult clinical problems. In this review, I have attempted to discuss clinically relevant issues pertaining to both hypo- and hyperthyroidism during pregnancy, and present some personal views to integrate both apparently opposite types of thyroid dysfunction into a global strategy for the systematic screening, diagnosis and management of these disorders.

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